

## New Usage for an Old Drug in Diabetic Neuropathy

### Value of Amphetamines for Symptomatic Relief

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**I**N six case studies of patients with diabetic neuropathy, the use of amphetamines provided effective symptomatic relief after other medications had failed. A review of the literature failed to disclose previous usage of amphetamine for this entity.

#### DESCRIPTION OF DISEASE

Polyneuritis due to diabetes mellitus is an uncommon but painful complication. Generally, the symptoms are similar to those of neuritis of any other origin, whether toxic, infectious, chemical, neoplastic, nutritional or of unknown etiology.

The pathologic changes within the axones and myelin sheaths of the peripheral nerves, and even within the central nervous system, are generally reversible, unless there is severe damage. Hence, many authorities feel that, with proper dietary and medical regulation (oral or insulin), diabetic neuropathy is almost always reversible. However, the length of time required for the alleviation of symptoms is considered extremely variable, from a few weeks to several years.

The chief complaint is severe pain, usually worse at night. It may be superficial or deep and of varying intensity.

Sensory symptoms predominate over motor, exhibiting tingling sensations, pins and needles feelings, burning (sometimes described as freezing sensations), and stabbing or knife-like pains that vary in intensity, location, or sequence from moment to moment. It seems consistent that, if the receptor endings for tactile sensations are damaged, as well as elements of the spinal cord, namely, the lateral spinothalamic tract carrying sensations of temperature and pain, these three sensory qualities may become distorted. With loss of epicritic sensitivity there may be areas of anesthesia or pruritus.

Motor symptoms consist of varying degrees of weakness and atony of smooth muscle, with loss of

function, followed by infection of the genito-urinary or gastrointestinal tracts. Deep tendon reflexes may be diminished or absent, especially the patellar and Achilles tendon<sup>1</sup> reflexes. Vibration sense may be lost or diminished. There are also vasomotor changes in diabetic neuropathy, such as hyperemia of the skin, pallor, dryness or else sweating, as well as trophic changes in the skin and nails, such as ulcerations, atrophy and ridged, brittle nails.

Various unusual complications of diabetic neuropathy have been reported including multiple arthropathy (Charcot's joint),<sup>2</sup> neuropathic fracture,<sup>3</sup> gastric atony,<sup>4, 5</sup> esophageal dysfunction occasionally with dysphagia,<sup>6</sup> and Dupuytren's contraction.<sup>7</sup>

#### TREATMENT

It is generally agreed that maintenance of a normal blood sugar level, adequate nutrition, and supplementation of the diet with multiple vitamins tends to delay occurrence of diabetic neuropathy and often improves the condition. However, some patients continue to worsen despite a proper regimen.<sup>8</sup>

Vitamin B<sub>12</sub> (cyanocobalamin) has been used empirically but there is little evidence that it shortens or changes the course of the disease.<sup>9</sup> Three investigators reported that there is a deficiency of vitamin B<sub>12</sub> and that injections are beneficial.<sup>10-12</sup> However, Goodman and Gilman<sup>13</sup> discredit this usage and I have not found it helpful in my practice.

The pain of diabetic neuropathy is often so severe that the patients demand narcotics for relief,<sup>14</sup> although they are contraindicated. Salicylates are ineffectual in this condition.

Recently, it was my experience to offer effective symptomatic relief (one method through an accidental occurrence) to six patients with this complication of diabetes. The drugs used were ethyl

chloride spray and various preparations of amphetamines. A survey of the medical literature disclosed no previous usage of these two drugs for relief of diabetic neuropathy.

Less than freezing applications of ethyl chloride have proved valuable as a form of counterirritation to relieve myofascial and visceral pain syndromes. The rationale is that protracted myofascial pain following activation of a trigger area depends on maintenance of a reflex pain cycle and that transitory local block of trigger areas may relieve the referred pain permanently.<sup>15</sup> Painful muscle spasm, including stiffneck, trismus, lumbago, sciatica, ankle and heel pain, tennis elbow and shoulder pain have also responded to this therapy.<sup>16</sup>

The amphetamines raise the threshold of pain in dogs.<sup>17</sup> Analgesia is also seen in humans,<sup>13</sup> particularly for relief of dysmenorrhea.<sup>16</sup> In my survey of literature I could find no reference to usage of amphetamines in diabetic neuropathy or related conditions.

#### TYPICAL CASE REPORTS

The first patient, a female, aged 61, visited my office for the first time on March 6, 1970. The second, a male, aged 48, started treatment one week later. The two case histories were notable, more for their similarities than their few differences, and will be discussed therefore as a unit.

The few salient points of difference between the two were that the man discovered his diabetes about 14 years previously but started treatment with his physician seven years later, while the woman knew of her diagnosis six years ago and promptly began treatment. Moreover, all oral agents were ineffective from the start with the man, who began treatment on diet plus insulin, whereas the woman started insulin after less than a year on oral medication, due to secondary failure. A maternal aunt of the man and the mother of the woman were known to have been diabetic.

In the early treatment of these patients, their physicians had elicited good results, judging from laboratory reports and the patients' feeling of well-being. Subsequently, as so often happens when the patient feels well, they paid little heed to their prescribed diets, finally neglecting even to take insulin. Occasionally, they would test their urine at home, which was generally reported as highly positive for glucose.

When seen for the first time, both patients reported severe pains and pins and needles paresthesia below the neck line, predominating in the legs, feet, the buttocks in the man and in the fingertips and wrists in the woman. The time of origin of the pain and paresthesia could not be approximated, coming on gradually until they were severe enough to require treatment. The man approximated the duration of the greatest distress at six

months and the woman about 10 months prior to seeking help. Occasionally, the man would develop short lasting severe pruritus about the pelvis and lower back. During the height of pain or tingling, motion would aggravate the symptoms in both cases. Progressive fatigability was also a dual complaint. Both patients at times could not describe whether they felt hot or cold but knew that it was one or the other.

On physical examination, a few abnormal findings in each were found, such as mild obesity and benign hypertension (in the man), none of which required immediate attention. In both cases blood sugar and urine reports indicated diabetes without acidosis, complicated by a typical neuropathy.

Along with diet, a number of the currently recommended agents were tried, singly and at other times concurrently. When the sugar chemistry was not markedly lowered, lente insulin was prescribed and in a few weeks the responses were satisfactory, except for pain and pins and needles feelings as at the start of treatment. The drugs tried were salicylates, high vitamin potencies (especially niacin), barbiturates, vitamin B<sub>12</sub> injections, muscle relaxants, and even antibiotics (on the theory that the latter might exert a pharmacologic action against inflamed nerve trunks). They were totally ineffective as were phenylbutazone and diphenylhydantoin, which have been used with reported success by some clinicians. The latter two drugs, along with indomethacin, an antihistamine and an antipruritic had to be stopped early, because the patients developed side-effects. The pains of diabetic neuropathy were not relieved by salicylates in any dosage.

In the interim, the greatest relief experienced was in taking warm baths, but the amelioration was partial and very temporary.

After exhausting the therapeutic possibilities, it occurred to me to consider the use of a topical anesthetic. If irritative and painful skin sensations were present, it would seem logical that an anesthetic spray might mask their perception, which was almost constant, and thereby break the vicious circle. Consequently, ethyl chloride was sprayed lightly over wide areas of maximum discomfort. This new use of an old agent offered worthwhile relief for periods varying from fifteen minutes to a few hours. The big disadvantage is that it is not safe for self use, requires multiple applications over too large a body area, and its effectiveness is only partial and not long lasting. Nevertheless it is worthy of experimental trial if a large case load of patients with diabetic neuropathies is available for study. At this time, ethyl chloride spray is not recommended for specific therapy but only to provide temporary relief.

Thus it was that there was nothing substantially effective that could be found with which to treat the patients until the man, justifiably depressed, suggested that he be given a prescription for amphetamine. Many years ago he had taken this drug as an anorexic agent. Since he was still slightly obese, it was given in low dosage. Much to my surprise he returned one week later with the unexpected statement that both the pains and paresthesia had markedly improved. Similarly, the woman was given a prescription for amphetamine with iden-

tical results.

In both cases amphetamine\* medication was used in gradually increasing dosage as needed for a period of more than four months with continued success. Four other cases had similar results.

#### RESULTS WITH AMPHETAMINES

From a study of the use of amphetamines given weekly to these four patients, suffering from diabetic neuropathy, the following observations were made: 1) The ideal dosage of amphetamine in any form is the least that offers relief. It is best to start with low dosage, gradually increasing. 2) Relief was estimated variously from 30 per cent to 90 per cent with proper dosage. 3) The dose must be "played by ear," increasing from week to week with the knowledge, for example, that a 5 mg. dose one week would be ineffective two weeks later. 4) The type of amphetamine used must frequently be changed to be effective, whether dextro-amphetamine, methamphetamine or other derivative is used. Therefore the same form of amphetamine should be used only temporarily. Later on the brand given some time before may be tried again, for it will regain its effectiveness after a lapse of time. A combination of amphetamines seems to be more effective than a single drug. 5) It is rarely if ever required to use more than one 20 mg. tablet per day (for example, one product recommends up to two tablets daily for obesity). 6) Not only do pains and paresthesias in the main disappear to a large extent for six to 24 hours, but along with it, general stamina, greater agility and mobility of joints occur. During the time of relief, motion no longer aggravates pain or paresthesia. 7) On rare occasion, the amphetamine used will offer no relief. At such times, an addition of a small dose of a different derivative will help greatly. 8) The side effects of slight euphoria and temporary anorexia are added bonuses and the rebound depression is mild and temporary when the dose of amphetamine is closely regulated.

#### SUMMARY

Numerous agents were tried on six patients with diabetic neuropathy, including drugs mentioned in the literature as offering relief. These were without apparent benefit.

Two official drugs, ethyl chloride and amphetamine, provided effective relief over a long period

of time. In a survey of the literature there were no references to the use of these drugs for diabetic neuropathy.

Various forms of amphetamine, especially when used in combination, effectively relieved the pain and paresthesia during a long period of medication. Results with amphetamine are highly successful when the drug is assiduously applied and studied in each individual case. Though its mechanism of action in this condition is not understood beyond the fact that it is a stimulant of the central nervous system and raises the threshold of pain perception, the results obtained in these six cases demand further trial. It is doubtful whether the relief afforded is embedded in a psychological core of euphoria produced by the drug, since the amelioration extends further in time than the temporary euphoria and anorexia that the drug produces.

While offering symptomatic relief, amphetamines may possibly bear relationship to the natural history of the remission in diabetic neuropathy by altering the pathways of pain reception. Careful dietary and insulin regulation are of course fundamental.

In view of the fact that treatment with low dosage amphetamines produced excellent relief of symptoms in the six diabetics described, it is conjectured that polyneuritis of any etiology may react in similar fashion. Hence a thorough clinical trial of this old and often maligned drug in non-diabetic neuropathies is warranted.

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\* Various preparations of amphetamines were prescribed, principally Obetrol tablets (methamphetamine saccharate 2.5 mg., methamphetamine hydrochloride 2.5 mg., amphetamine sulfate 2.5 mg., dextroamphetamine sulfate 2.5 mg.).

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**COLOR AND PEOPLE: THE STORY OF PIGMENTATION.** By Marguerite Rush Lerner, M.D. 55 pp., illustrated. Minneapolis: Lerner Publications Company, 241 First Ave., North (55401), 1971. \$4.50.

This little book is a veritable gem. The author, an authority on the subject of pigmentation and an associate clinical professor at the Yale University School of Medicine, has written a straightforward, easily understandable yet scientifically accurate and not-overly simplified account of skin pigmentation. Dr. Lerner explores the role of melanin pigment in animal and human skin. She explains the mechanisms of pigment camouflage in frogs, reptiles and mammals, telling in clear, lucid prose how the color change takes place. She also discusses other subjects concerned with pigmentation such as skin spots, moles, suntan and sunburn and the pigmentation of the skin, hair and eyes. There is even a discussion of what happens to skin color of the offspring in human black-white marriages.

A most engaging feature of this delightful little book is the way the author has generously sprinkled carefully-chosen, first-rate color illustrations throughout the text

discussion. This does much to add life to the material and to emphasize its message. The book ends with a speculative and philosophical chapter on "Why Melanin?" in which the author considers teleological reasons for the existence of melanin.

So interestingly presented and written is the entire subject that one might only wish for more, that the book were larger. But perhaps this would have spoiled its impact, making it too long for younger readers and distorting the author's intention. For Dr. Lerner has succeeded in writing an admirable, eminently readable up-to-date and concise account of what could be an otherwise esoteric and difficult subject. This little volume will be treasured by all who turn to it for an appreciation of the subject of pigmentation. Certainly today when the subject of skin pigmentation is so much in the limelight and possesses such far-reaching sociological and emotional implications and connotations, a clear, dispassionate discussion of the subject is more than welcome. This book should be made available to older children and to adults. It is highly recommended.

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